# Cefuroxime selective electrodes for batch and FIA determinations in pharmaceutical preparations[1]

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## Abstract

Different cefuroxime selective electrodes, without internal reference solution and comprising PVC membranes, were constructed and evaluated. Membranes were prepared with cefuroxime tetraoctylammonium (A) or cefuroxime bis(triphenylphosphoranylidene)ammonium (B) as ion-exchanger, 2-nitrophenyl octyl ether (X) or bis(2-ethyl-hexyl)sebacate (Y) as plasticizing mediator solvent and 4-tert-otcylphenol (TOP) as additive. From the comparative evaluation of the described electrodes, membranes comprising 2-nitrophenyl octyl ether, cefuroxime tetraoctylammonium and 4-tert-otcylphenol presented better working characteristics. For these electrodes (type XA-TOP), with a lifetime > 5 months, a lower limit of linear range of $2.8 \times 10^{-4}$ M, a practical detection limit of $1.3 \times 10^{-4}$ M, a reproducibility of $\sim \pm 0.6$ mV day$^{-1}$ and a slope of $-50.4$ mV decade$^{-1}$, under $H_3PO_4/NaH_2PO_4$ solutions (pH 3.5; I = 0.1 M), were found. The presence of the additive on the membranes was of crucial importance for the electrodes good characteristics. Interference from sulphate, chloride, nitrate, iodide, cefaclor, cefadroxil, cefazolin and cephradine, on the electrodes behaviour was evaluated. Only a slight interference from nitrate and iodide was recorded, being type XA-TOP electrodes the most selective units. Electrodes with a tubular configuration prepared with type XA-TOP membranes, aiming flow injection analysis, were also constructed. When these tubular potentiometric detectors were evaluated in a double-channel flow injection manifold, with 3.5 pH and 0.1 M ionic strength conditions, significantly better working characteristics than those of the corresponding conventional electrodes, namely higher slopes ($-54.6$ mV decade$^{-1}$) and better reproducibilities ($\pm 0.2$ mV day$^{-1}$), were found. Both conventional and tubular type XA-TOP electrodes were used for injections analyses by batch and FIA, respectively, presenting low consumption of samples and reagents. Relative error deviations to the reference procedures < 3.0% were found. © 1998 Elsevier Science B.V. All rights reserved.

*Keywords:* Cefuroxime; Pharmaceutical preparations; Ion-selective electrodes; Potentiometry; Cephalosporin; FIA

## 1. Introduction

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Cefuroxime (CFX) is a semisynthetic $\beta$-lactam antibiotic of the cephalosporin group, intended for parenteral administration only, for its negligible intestinal absorption. CFX for injection is

presented as the sterile sodium salt in a sealed container, prepared by the addition of the appropriated volume of sterile water [1].

Several works referred to in literature [1–3], as well as the US Pharmacopoeia (USP) Cefuroxime sodium (CFX.Na) injection monograph [4], resort HPLC procedures with a spectrophotometric detection, usually applied to the analysis of industrial batches of CFX.Na. Despite being an old-standing and well known methodology, usually using short retention times, and previously found in good agreement with the old microbiological assay [5], HPLC procedures require sophisticated and expensive instruments, a specific column for each determination and special care with reagents before its injection into the chromatographic system (filtration and degassing).

Furthermore, spectrophotometric and fluorimetric procedures, involving long sample pretreating times with heat [6,7], polarographic procedures, requiring the use of a highly toxic compound like mercury [8–10], and near infrared reflectance spectroscopy procedures, characterized by a small calibration range [11], are also found in literature.

Without all of these drawbacks and presenting high analytical ranges and reproducibilities, minimal interference from associated and related species, direct application to turbid and coloured drug solutions without any pre-treatment and low cost and easy operation of the potentiometric instrumentation, direct potentiometry using conventional ion selective electrodes (ISEs) is nowadays a highly desirable alternative for the analysis of pharmaceutical compounds [12]. Additionally, by selecting both a convenient sensor system and a suitable electrodes construction method [13], it is further possible to perform automatic analyses by using electrodes with a tubular configuration in simple flow injection analysis (FIA) systems. These procedures enable high sampling rates, without specific samples pre-treatment, low consumption of samples and reagents, and give rise to precise results [14–21].

Despite several ISEs for the determination of cephalosporins, as the ones for chephalothin and cephalexin, have been referred in literature [22–24], only one potentiometric cefuroxime determination, based on an indirect and small specific procedure, requiring a previous sample neutralization for 10 min with hydroxylamine and the use of toxic reagents like $Hg(ClO_4)_2$, is described [25]. Therefore, aiming a direct potentiometric analysis of pharmaceutical preparations, CFX selective electrodes were constructed and evaluated. Different sensor systems were tested, and the most adequate was selected both for conventional and FIA CFX.Na determinations in the commercially available pharmaceutical preparations.

## 2. Experimental

### 2.1. Apparatus

A Crison 2002 µpH potentiometer (sensitivity $\pm 0.1$ mV) coupled to an Orion 605 switcher was used for measuring the potential differences between a Orion 90-02-00 double junction AgCl/Ag reference electrode and the indicator electrode.

The pH measurements were performed with a Russel SWL glass electrode. Its calibration, aiming the $pK_a$ determination, was carried out using the Gran Method [26]. All $pK_a$ determinations were carried out under nitrogen atmosphere, at 25°C, with a Metrohm EA-876-20 double-walled glass cell, a Julabo EM74 thermostated bath and a computer controlled Crison 2031 burette.

For FIA determinations, a Gilson Minipuls 3 peristaltic pump, a four-way Rheodyne 5020 rotating valve, a Kipp and Zonen BD111 recorder and several home-made perspex devices, namely confluences, reference and tubular electrode supports [27], joined together by Teflon tubing (0.8 mm i.d.), were used.

### 2.2. Reagents and solutions

All reagents were of analytical grade without additional purification. Tetraoctylammonium bromide (TOA.Br, Fluka), bis(triphenylphosphoranylidene)ammonium chloride (TPPIA.Cl,

Aldrich), CFX.Na (Sigma, St. Louis, MO), cefaclor (Sigma), cefadroxil (Sigma), cefazolin (Sigma), cephradine (Sigma) and sodium hydroxide (NaOH, Riedel-deHaen) were used.

For the electrode membrane preparation, 2-nitrophenyl octyl ether (oNFOE, Fluka), bis(2-ethylhexyl)sebacate (BEHS, Fluka), 4-tert-otcylphenol (TOP, Fluka), Poly (vinylchloride) of high molecular weight (PVC, Fluka) and Tetrahydrofuran (THF, Riedel-deHaen) were used.

The most concentrated solutions were prepared by carefully weighing and diluting the corresponding solids with de-ionised water (conductivity < 0.1 $\mu S$ cm$^{-1}$). The less concentrated solutions were obtained by dilution of the previous ones. All solutions were prepared daily, as they are stable at room temperature for only 13 h [28].

When the conventional and tubular electrode characteristics were evaluated under ionic strength adjustment conditions, a 0.033 M $Na_2SO_4$ solution (I = 0.1 M) was chosen, according to the interference levels of the comprised chemical species. Regarding the conventional electrodes evaluation under simultaneous pH and ionic strength adjustments, and in agreement with the electrodes operational pH ranges, a $H_3PO_4$/$NaH_2PO_4$ solution (pH 3.5; I = 0.1 M) was selected. This previous solution, used for standards and samples dilution, ensured the same ionized/non ionized ratio of CFX in solution. Regarding the tubular electrodes evaluation under pH and ionic strength adjustments, all standard and sample solutions were prepared by dilution with water, as the FIA systems allowed all the necessary adjustments inside the manifold (Fig. 1(b)) by using the appropriate carriers.

## 2.3. Cefuroxime sodium $pK_a$ determination

As CFX acidity constant was not mentioned in the literature, its determination was required. Therefore, data analysis from six independent titrations with NaOH ( ∼ 0.1 M), under 0.1 M ionic strength conditions, was performed by using the Superquad computer program [29]. An average $pK_a$ of 2.28 with a 0.02 standard deviation was obtained.

## 2.4. Conventional and tubular electrodes construction

For CFX selective electrode construction, different ion-exchangers and mediator solvents were used aiming for the selection of a sensor system that would provide good working characteristics. Considering the mediator solvents dielectric constant influence on the electrodes selectivity characteristics, very different plasticizing mediator solvents were selected (oNFOE-20.6 and BEHS-4.01) [30]. Furthermore, the addition of TOP to the membranes was also pondered for improving the working characteristics of carboxylate selective electrodes [31]. The effect of TOP uses to reveal itself by an enhancing of the electrodes selectivity characteristics, which is explained by the hydrogen bonding between the phenol and the carboxylate anion. The stronger the interaction with the phenolic proton, the more effective is the enhancement of the selectivity. Carboxylate anions have relatively stronger proton-acceptor ability than inorganic anions, being the degree of change in the logarithmic selectivity coefficient related to the proton acceptor ability of each interfering ion.
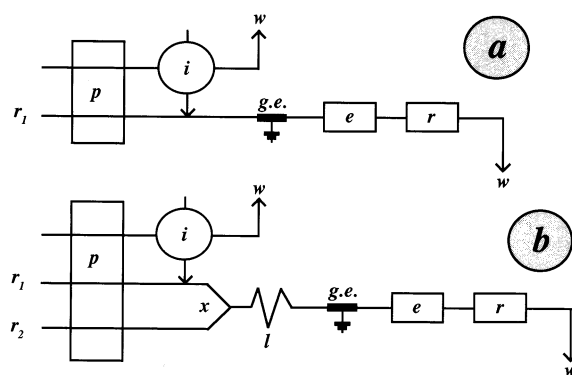


Fig. 1. Flow injection low dispersion manifold used for tubular electrode evaluation (a) and for CFX.Na determinations in pharmaceutical preparations (b). p, peristaltic pump; i, injection valve (loop 570 $\mu$l); g.e, grounding electrode; l, length (20 cm); e, tubular electrode (type XA-TOP); r, reference electrode; w, waste; $r_1$, carrier (0.033 M $Na_2SO_4$ solution for a and de-ionised water for b); $r_2$, carrier ($H_3PO_4$/$NaH_2PO_4$ solution—pH 3.5; I = 0.1 M). The total flow rate was 6.0 ml min$^{-1}$.

Table 1
Membrane composition (% w/w) of the several types of conventional CFX selective electrodes

| Components | Electrodes type | | | |
| --- | --- | --- | --- | --- |
| | XA-TOP | YA-TOP | XB-TOP | YB-TOP |
| CFX.TOA | 1.4 | 1.4 | — | — |
| CFX.TPPIA | — | — | 1.3 | 1.3 |
| oNFOE | 62.4 | — | 60.9 | — |
| BEHS | — | 62.6 | — | 60.9 |
| TOP | 7.4 | 7.1 | 7.6 | 7.5 |
| PVC | 28.8 | 28.9 | 30.2 | 30.3 |

The CFX tetraoctylammonium (CFX.TOA) ion-exchanger (A) was obtained by extraction with a solution of approximately 0.027 g of TOA.Br in 2 g of oNFOE (type XA) or BEHS (type YA), to which $CHCl_3$ has been added to increase the volume and therefore facilitate the extraction, and $3 \times 50$ ml of a 0.01 M CFX.Na aqueous solution. After the two phase separation and the $CHCl_3$ evaporation, the sensor solutions were kept with anidrous sodium sulfate in a dark place.

The CFX bis(triphenylphosphoranylidene)ammonium (CFX.TPPIA) ion-exchanger (B) was obtained by a precipitation reaction between 50 ml of a 0.01 M CFX.Na aqueous solution and 100 ml of a 0.01 M TPPIA.Cl aqueous solution. The resulting precipitate was filtered, flushed with deionized water, dried and kept, protected from light, in a desiccator. The sensor solutions were obtained by dissolving $\sim 0.04$ g of the dried precipitate in $\sim 2$ g of oNFOE (type XB) or BEHS (type YB).

The different membrane electrodes (types XA-TOP, XB-TOP, YA-TOP and YB-TOP) were prepared by mixing 0.25 g of TOP in 0.4 ml of the corresponding sensor solutions with 0.18 g of PVC, previously dissolved in $\sim 6$ ml of THF. The relative composition of the different membranes is indicated in Table 1.

Previously described procedures were used for the construction of the conventional configuration electrodes [13] and the tubular detectors [32], ap-

plying dropwise the sensor membranes over a graphite and epoxy resin support.

## 2.5. Samples preparation

For the samples preparation, only dilutions in order to fit the commercially available pharmaceutical preparations (Curoxime® injection) CFX.Na content into the linear operational concentration range of the used electrodes were required. In agreement with the conventional electrodes operational pH ranges, dilutions were accomplished with a $H_3PO_4/NaH_2PO_4$ solution (pH 3.5; 0.1 M). As the necessary pH and ionic strength adjustments were achieved inside the FIA manifold (Fig. 1(b)), de-ionized water was used for the potentiometric analysis with the tubular detectors.

Therefore, samples were first diluted in a 25.0 volumetric flask, presenting a CFX.Na concentration of $\sim 7.1 \times 10^{-2}$ M. The potentiometric measurements were performed over an $\sim 2.5 \times 10^{-3}$ M concentration, obtained by diluting 0.9 ml of the previous solution in a 25.0 ml volumetric flask. As the simultaneous analysis of the same sample by the conventional electrodes, tubular electrodes and reference procedures was impracticable, recoveries over the potentiometric analysis were performed by adding 0.7 ml of a 0.15 M CFX.Na standard solution to 0.9 ml of the first sample dilution in a 25 ml volumetric flask.

For the CFX.Na injection USP official monograph [4], samples and standards dilution with mobile phase (mixture of 3.4 pH acetate buffer and acetonitrile) was required. The sample concentrations were determined after HPLC separation by spectrophotometric detection at 254 nm.

## 3. Results and discussion

### 3.1. Behaviour of the conventional cefuroxime selective electrodes

The general working characteristics of the conventional electrodes were first evaluated under 0.1 M ionic strength in a CFX.Na concentration range $1 \times 10^{-5} – 1 \times 10^{-1}$ M, by repeated calibra-

tion curves using the known addition method [33]. Under these conditions, despite the similar characteristics showed by the different electrodes (Table 2), those constructed with oNFOE membranes could be pointed out for having higher slopes and inferior lower limit of linear ranges (LLLRs) than those presenting BEHS membranes. Hence, types XA-TOP and XB-TOP electrodes were selected for further evaluations.

The addition of TOP to the electrodes membranes revealed itself of crucial importance, considering the deficient working characteristics of CFX electrodes with membranes without the referred additive (types XA, XB, YA, YB). These electrodes presented very low slopes (within 17–25 mV decade$^{-1}$) and poor reproducibilities, inadequate characteristics for CFX determinations by direct potentiometry.

Aiming the study of the pH influence on the type XA-TOP and XB-TOP electrodes, their potential changes versus the pH of a $5 \times 10^{-3}$ M CFX.Na solution with a 0.1 M ionic strength were recorded. The pH changes were obtained by the manual addition of small volumes of sodium hydroxide and sulphuric acid concentrated solutions and recorded with a glass electrode. From the Reilley diagrams presented in Fig. 2, operational pH ranges of $\sim 3.0$–4.0 and 2.3–4.9 were found for type XA-TOP and XB-TOP electrodes, respectively. The small opera-

tional pH ranges are not only due to the chemical characteristics of the primary ion but also to a possible occurrence of the phenolate anion, resulting from TOP [34]. With the increase of the pH values, a decrease on the electrodes potential was recorded, which was further due to a hydroxide anion interference. For pH values under $\sim 2.3$ (CFX.Na p$K_a$), the decrease on the ionized/non ionized ratio of CFX became perceptible (increase of the electrodes potential) and was followed by an abrupt decrease of the potential values, probably related to the appearance of the $HSO_4^-$ anion in solution.

Knowing the operationally usable pH ranges of the electrodes, the selection of the appropriate pH for a more accurate determination of their working characteristics was enabled. Therefore, when type XA-TOP and XB-TOP electrodes were evaluated in 3.5 pH and 0.1 M ionic strength conditions, with a $H_3PO_4$/NaH$_2$PO$_4$ solution, higher sensitivity, with $-50.4$ and $-44.4$ mV decade$^{-1}$, respectively, and lower LLRs and practical detection limits (PDLs) (magnitude of $10^{-4}$ M) were recorded (Table 3).

The interference extent of several inorganic cations and other cephalosporins on the type XA-TOP and XB-TOP electrodes behaviour was evaluated determining the potentiometric selectivity coefficients (log $K^{POT}$) by the separated

Table 2
Working response characteristics for conventional CFX selective electrodes under ionic strength adjusted to 0.1 M with a 0.033 M Na$_2$SO$_4$ solution

| Characteristics | Electrodes type | | | |
| --- | --- | --- | --- | --- |
| | XA-TOP | YA-TOP | XB-TOP | YB-TOP |
| Linearity range (M) | $2.0 \times 10^{-3}/1.0 \times 10^{-1}$ | $4.3 \times 10^{-3}/1.0 \times 10^{-1}$ | $1.7 \times 10^{-3}/1.0 \times 10^{-1}$ | $2.9 \times 10^{-3}/1.0 \times 10^{-1}$ |
| PDL (M)[a] | $1.5 \times 10^{-3}$ | $1.5 \times 10^{-3}$ | $1.2 \times 10^{-3}$ | $9.5 \times 10^{-4}$ |
| Slope (mV decade$^{-1}$)[b] | $-38.5 \pm 1.3$ | $-26.5 \pm 1.5$ | $-36.2 \pm 1.3$ | $-23.0 \pm 1.5$ |
| $R^{2c}$ | $>0.9990$ | $>0.9960$ | $>0.9979$ | $>0.9959$ |
| Reproducibility (mV day$^{-1}$) | $\pm 0.3$ | $\pm 0.5$ | $\pm 0.6$ | $\pm 1.9$ |
| Response time (s) | $<30$ | $<30$ | $<30$ | $<30$ |

[a]PDL, practical detection limit.
[b]Mean and standard deviation of four determinations with four electrodes.
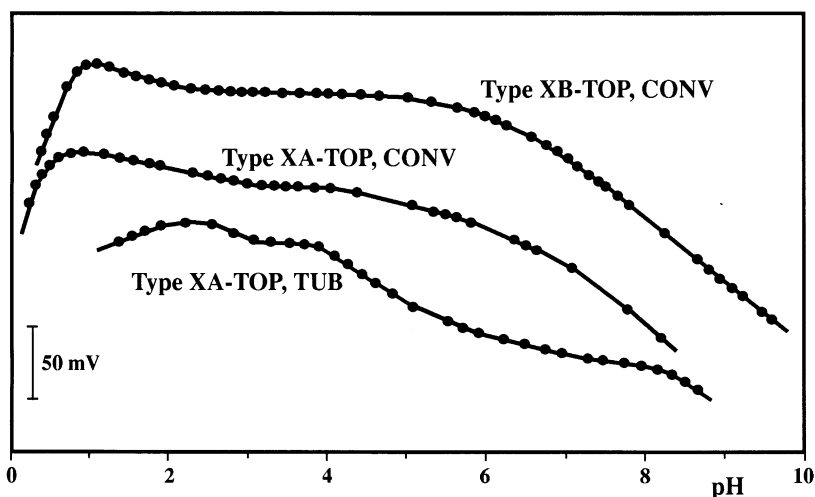[c]Square correlation coefficient of four determinations with four electrodes.

Fig. 2. pH profiles vs. potential for types XA-TOP and XB-TOP conventional (CONV) and type XA-TOP tubular (TUB) electrodes using $5 \times 10^{-3}$ M CFX.Na solutions.

solutions method [33] with interfering and primary ion concentrations of $1 \times 10^{-3}$, $5 \times 10^{-2}$ e $1 \times 10^{-2}$ M. Under these conditions, a similar behaviour for both types of electrodes was found. Results regarding $5 \times 10^{-2}$ M solutions are plotted in diagram 1, indicating a slightly higher selectivity for type XA-TOP electrodes.

The ISEs lifetime was evaluated considering the variations on the slope and reproducibility characteristics. As no significant change in these parameters was recorded while the electrodes were being used, their lifetime was estimated in more than five months (Table 3). This long lifetime was
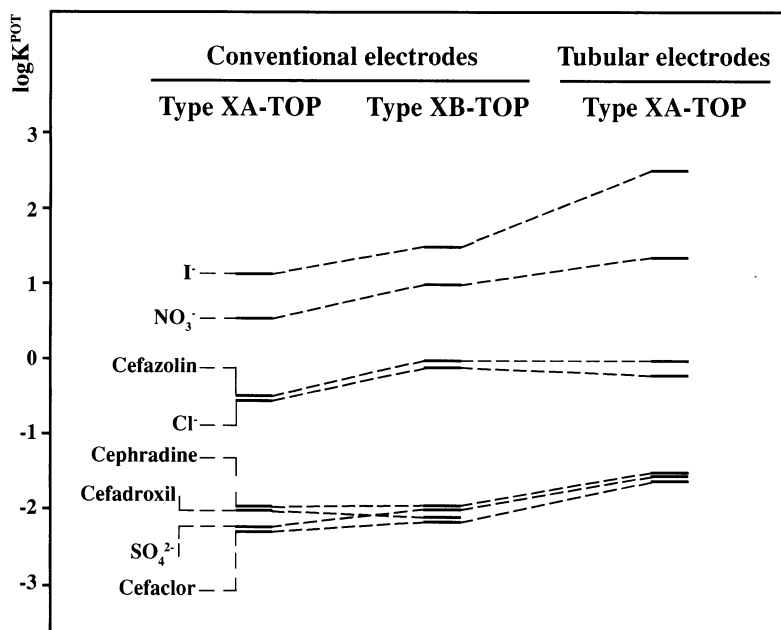
not surprising considering the used construction procedures [35].

As the better CFX selective electrodes working characteristics were obtained when the sensor system was established with CFX.TOA, oNFOE and TOP, type XA-TOP membrane was selected for the tubular electrodes construction.

## 3.2. Behaviour of the tubular cefuroxime selective electrodes

The type XA-TOP tubular detectors were first evaluated in a low dispersion single channel FIA manifold (Fig. 1(a)) by injecting CFX.Na standard solutions with 0.1 M ionic strength into the system through the injection valve (i). In order to reproduce the previous conventional electrodes evaluation conditions as much as possible, a 0.033 M $Na_2SO_4$ solution was used as carrier ($r_1$), which also had a CFX.Na concentration of $1 \times 10^{-7}$ M in order to stabilize the base line. By an univaryingly optimization process of the several FIA parameters, an injection volume of 570 μl (i), a flow rate of 6.0 ml min$^{-1}$ and a 20 cm coil (l), conditions leading to a 95% analytical signal of

the corresponding steady state, were chosen. Under these conditions, and comparing with the corresponding conventional electrodes, improvements were achieved on the tubular detectors main working characteristics, namely a slope increase ($-38.5$ to $-42.3$ mV decade$^{-1}$) and a slight betterment in reproducibility (Tables 2 and 3).

For the study of the pH influence on the tubular detectors behaviour, a manifold similar to the single channel system but with small modifications [36] and $5 \times 10^{-3}$ M CFX.Na solutions with 0.1 M ionic strength were used. An operational pH range 3.0–4.0 was found, which is in agreement with the corresponding conventional electrodes behaviour.

The tubular detectors selectivity characteristics were evaluated using a procedure similar to the separated solutions method [36] in the single channel manifold and in regard to the same interfering species and to the same concentration levels studied for the conventional electrodes. The determined potentimetric selectivity coefficients were similar to the ones obtained with the corresponding conventional electrodes (see diagram 1).

Table 3
Working response characteristics for conventional CFX selective electrodes in $H_3PO_4$/$NaH_2PO_4$ solutions (pH 3.5; 0.1 M) and with type XA-TOP tubular electrodes in single and double channel FIA systems

| Characteristics | Conventionally-shaped | | Tubular | |
| --- | --- | --- | --- | --- |
| | XA-TOP | XB-TOP | Type XA-TOP | |
| | | | Single chanel[e] | Double channel[f] |
| Linearity range (M) | $2.8 \times 10^{-4}/1.0 \times 10^{-1}$ | $4.5 \times 10^{-4}/1.0 \times 10^{-1}$ | $2.0 \times 10^{-3}/1.0 \times 10^{-1}$ | $4.0 \times 10^{-4}/1.0 \times 10^{-1}$ |
| PDL (M)[a] | $1.3 \times 10^{-4}$ | $3.0 \times 10^{-4}$ | — | — |
| Slope (mV decade$^{-1}$)[b] | $-50.4 \pm 1.4$ | $-44.4 \pm 0.8$ | $-42.3 \pm 0.3$ | $-54.6 \pm 0.4$ |
| $R^{2c}$ | >0.9996 | >0.9969 | >0.9981 | >0.9991 |
| Reproducibility (mV day$^{-1}$) | $\pm 0.6$ | $\pm 0.7$ | $\pm 0.2$ | $\pm 0.2$ |
| Response time (s) | <20 | <20 | — | — |
| pH working range[d] | 3.0–4.0 | 2.3–4.9 | 3.0–4.0 | — |
| Sampling rate (samples h$^{-1}$) | — | — | — | ~130 |
| Lifetime (months) | >5 | >5 | >5 | |

[a]PDL, practical detection limit.
[b]Mean and standard deviation of four determinations with four electrodes.
[c]Square correlation coefficient of four determinations with four electrodes.
[d]In $5 \times 10^{-3}$ M CFX.Na solutions with ionic strength adjusted to 0.1 M with 0.033 M $Na_2SO_4$ solutions.
[e]Under 0.1 M ionic strength adjustment.
[f]Under simultaneous pH and ionic strength adjustment to 3.5 and 0.1 M, respectively.

The tubular detectors main working characteristics were also evaluated under pH and ionic strength values of 3.5 and 0.1 M, respectively, achieved automatically inside the established double channel FIA system (Fig. 1(b)). Thus, carrier $r_2$ comprised a $H_3PO_4/NaH_2PO_4$ (pH 3.5; 0.2 M) solution with $2 \times 10^{-7}$ M in CFX.Na, having twice the concentration of the ones used in the single channel system, and was diluted approximately by half at the confluence point ($x$) with the $r_1$ carrier solution (de-ionised water). In order to guarantee the adequate mixture of the two carriers, several coil lengths were tested maintaining the other FIA parameters (570 µl injection volume ($i$) and an overall flow of 6.0 ml min$^{-1}$). A 20 cm coil ($l$) was selected for complying with the purpose without increasing the dispersion. Under these conditions, sampling rates of $\sim 130$ samples h$^{-1}$ were obtained.

The tubular detectors lifetime (Table 3) was found equal to the corresponding conventional electrodes, according to the same criteria.

### 3.3. Analysis of cefuroxime sodium injections

The potentiometric analysis of Curoxime® injection, the only available pharmaceutical preparation containing CFX.Na, was carried out with the type XA-TOP conventional electrodes, by batch, and with their corresponding tubular detectors, by FIA. In Fig. 3, a typical diagram of the injection of CFX.Na standard solutions (electrodes calibration, I–V) and a diluted sample (VI) with its recovery (VII) is plotted. The values obtained from the potentiometric analysis (averages of CFX.Na concentrations and recoveries, with the corresponding standard deviations), as well as those from the USP reference procedures [4], are indicated in Table 4. Results of the USP procedures are the average values from the analysis of commercial samples specified with the same industrial batch as the ones analysed potentiometrically.

All sample analysis were in agreement with the USP procedures and gave good recovery values. The small relative error deviation between the potentiometric and the USP analysis showed a good accuracy for the both conceived potentio-
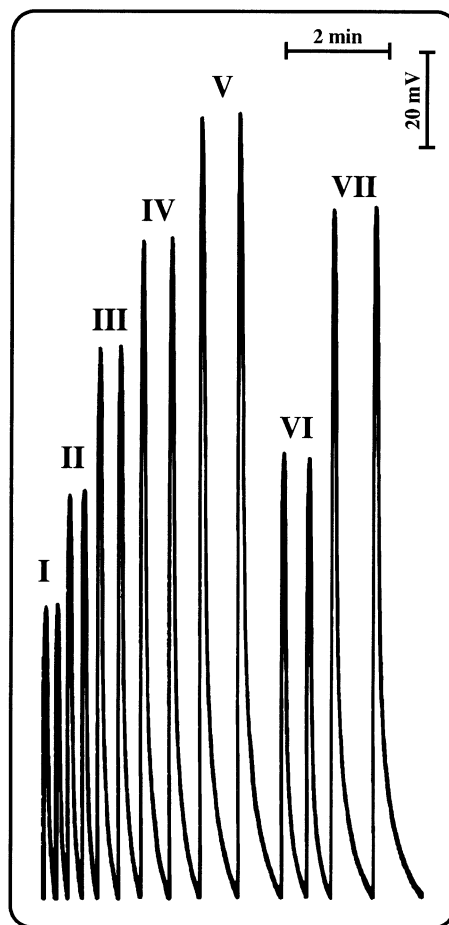


Fig. 3. FIA register obtained with the tubular electrodes (type XA-TOP) by the injection of different standard CFX.Na solutions (I = $1.3 \times 10^{-3}$ M; II = $2.0 \times 10^{-3}$ M; III = $4.0 \times 10^{-3}$ M; IV = $6.0 \times 10^{-3}$ M; V = $1.0 \times 10^{-2}$ M), a diluted solution of Curoxime® injection (VI) and its recovery (VII), for the determination of the CFX.Na content on this pharmaceutical preparation.

metric methodologies, batch with the type XA-TOP conventional electrodes and FIA with the corresponding tubular detectors.

### 4. Conclusions

The present work points out the importance of the selection of a suitable sensor system in order to obtain electrodes with good working characteristics. After a systematic study of several ones,

Table 4
CFX.Na determination in pharmaceutical preparations using conventional and tubular type XA-TOP CFX selective electrodes and the corresponding USP monograph

| Pharmaceutical preparation (nominal content, g/inj.) | Conventional | | USP[b] | Tubular | | USP[c] |
|---|---|---|---|---|---|---|
| | Found (g inj.$^{-1}$) | Recovery (%) | Found (g inj.$^{-1}$) | Found (g inj.$^{-1}$) | Recovery (%) | Found (g inj.$^{-1}$) |
| Curoxime® inj. (0.79) | $0.92 \pm 0.02$ | $99.8 \pm 0.5$ | $0.89 \pm 0.03$ | $0.85 \pm 0.05$ | $100.0 \pm 1.2$ | $0.83 \pm 0.02$ |

Nominal values between parenthesis; mean and standard deviation of eight determinations with three electrodes.
[a]According to USP, contains no less than 90.0% and no more than 120.0% of the labeled amount.
[b]Analyses of the same batch used for the conventional electrodes.
[c]Analyses of the same batch used for the tubular electrodes.

prepared with different structure ammonium salts and dielectric constant mediator solvents, and therefore leading to dissimilar selectivity and sensitivity characteristics, it was possible to obtain appropriate electrodes for both simple and accurate analysis of CFX pharmaceutical preparations. For CFX selective electrodes it was shown that, independently from the existing ion-exchanger, oNFOE mediator solvent gave rise to better electrodes working characteristics than BEHS. Furthermore, the presence of a proton donor additive (TOP) on the sensor system turned out to be essential, considering the deficient characteristics of CFX selective electrodes constructed without it.

The selected construction method of the conventional electrodes, characterized by the absence of an internal reference solution, led to easy handling and robust units, with long lifetimes. Furthermore, it permitted the evaluation of the same sensor system under flow conditions by using miniaturized similar electrodes (tubular detectors), with the adequate configuration for FIA systems. Under these conditions, an increase in sensitivity was recorded and a sampling rate of 130 samples $h^{-1}$ was achieved, due to the low tubular detectors response time.

When compared to the USP procedure, which is quite expensive for requiring sophisticated HPLC instruments and a specific column, the proposed potentiometric alternative procedures become advantageous, not merely for the speed of the analyses, specially those performed with the tubular detectors, but also for the simplicity, low cost and easy handling of the used analytical devices.

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## References

[1] P.A. Coomber, J.P. Jefferies, J.D. Woodford, Analyst 107 (1982) 1451–1456.
[2] V. Quercia, C. Sena, P. Gambero, G. Pagnozzi, N. Pierini, M Terracciano, Boll. Chim. Farm. 118 (1979) 308–315.
[3] W. Xue, G. Zhong, X. Hu, Yaowu Fenxi Zazhi 16 (1996) 95–97.
[4] United States Pharmacopoeia XXIII, United States Pharmacopoeial Convention: Rockville, MD, 1995, pp. 317.
[5] V. Springolo, G. Coppi, Boll. Chim. Farm. 122 (1983) 104–108.
[6] P.B. Issopoulos, Analyst 114 (1989) 237–239.
[7] J.A. Murillo, J.M. Lemus, L.F. García, J. Pharm. Biomed. Anal. 12 (1994) 875–881.
[8] F.I. Sengun, K. Ulas, I. Fedai, J. Pharm. Biomed. Anal. 3 (1985) 191–199.
[9] B. Ogorevc, V. Hudnik, S. Gomiscek, Fresenius'Z Anal. Chem. 330 (1988) 59–64.
[10] G. Bernacca, L. Nucci, F. Pergola, Electroanalysis 6 (1994) 327–332.
[11] P. Corti, E. Dreassi, G. Ceramelli, S. Lonardi, R. Viviani, S. Gravina, Analysis 19 (1991) 198–204.
[12] K. Vytras, J. Pharm. Biomed. Anal. 7 (1989) 789–812.
[13] R.A.S. Lapa, J.L.F.C. Lima, A.M.R. Silva, Il Farm. 45 (1990) 901–913.
[14] J.L.F.C. Lima, M.C.B.S. Montenegro, J. Alonso, J. Bartroli, J.G. Raurich, J. Pharm. Biomed. Anal. 7 (1989) 1499–1505.
[15] J.L.F.C. Lima, M.C.B.M. Montenegro, A.M.R. Silva, J. Flow Inj. Anal. 7 (1990) 19–33.
[16] J.L.F.C. Lima, M.C.B.S.M. Montenegro, J. Alonso, J. Bartroli, J.G. Raurich, Anal. Chim. Acta 234 (1990) 221–225.
[17] J.L.F.C. Lima, M.C.B.S.M. Montenegro, A.M.R. Silva, J. Pharm. Biomed. Anal. 9 (1991) 1041–1046.
[18] J.L.F.C. Lima, M.C.B.S.M. Montenegro, J.A. Chamarro, J. Bartroli, J.G. Raurich, Anal. Sci. 8 (1992) 19–23.
[19] M.N.M.P. Alçada, J.L.F.C. Lima, M.C.B.S.M. Montenegro, J. Pharm. Biomed. Anal. 13 (1995) 459–464.
[20] J.L.F.C. Lima, M.C.B.S.M Montenegro, M.G.F. Sales, J. Pharm. Biomed. Anal. 14 (1996) 931–938.
[21] J.L.F.C. Lima, M.C.B.S.M Montenegro, M.G.F. Sales, J. Pharm. Sci. 80 (1997) 1234–1238.
[22] L. Campanella, F. Mazzei, R. Sbrilli, M. Tomassetti, Ann. Chim. 80 (1990) 395–412.
[23] L. Campanella, F. Mazzei, R. Sbrilli, M. Tomassetti, J. Pharm. Biomed. Anal. 6 (1988) 299–305.
[24] L. Campanella, M. Tomassetti, F. Mazzei, R. Sbrilli, J. Pharm. Biomed. Anal. 6 (1988) 717–723.
[25] B. Pospisilova, J. Kubes, Pharmazie 43 (1988) 246–248.
[26] G. Gran, Analyst 77 (1952) 661–671.
[27] S. Alegret, J. Alonso, J. Bartroli, A.A.S.C. Machado, J.L.F.C. Lima, J.M. Paulis, Quim. Anal. 6 (1987) 278–294.

[28] S. Budavari (Ed.), Index Merck, An encyclopedia of chemicals, drugs and biologicals, 11th edn., Merck, Rahway, N.J., 1989, pp. 948–949.

[29] P. Gans, A. Sabatini and A. Vacca, J. Chem. Soc. Dalton Trans. (1985) 1195–1200.

[30] T. Okada, H. Sugihara, K. Hiratani, Analyst 120 (1995) 2381–2386.

[31] T. Fujinaga, Phil. Trans. R. Soc. Lond. A305 (1982) 631–635.

[32] S. Alegret, J. Alonso, J. Bartroli, J. M. Paulis, J.L.F.C. Lima, A.A.S.C. Machado, Anal. Chim. Acta 164 (1984) 147–152.

[33] IUPAC, Analytical chemistry division commission on analytical nomenclature, recommendations for publishing manuscripts on ion-selective electrodes, Pure Appl. Chem. 53 (1981) 1907–1912.

[34] H. Hara, Y. Kondoh, O. Mitani, S. Okasaki, Anal. Chem. 62 (1990) 1139–1143.

[35] G.J. Moody, J.D.R. Thomas, J.L.F.C. Lima, A.A.S.C. Machado, Analyst 113 (1988) 1023–1027.

[36] S. Alegret, J. Alonso, J. Bartroli, J.L.F.C. Lima, A.A.S.C. Machado, J.M. Paulis, Anal. Lett. 18 (1985) 2291–2303.